Prospective Study of Fruit and Vegetable Consumption and Risk of Lung Cancer Among Men and Women

Diane Feskanich, Regina G. Ziegler, Dominique S. Michaud, Edward L. Giovannucci, Frank E. Speizer, Walter C. Willett, Graham A. Colditz

Background: **Diets high in fruits and vegetables have been shown to be associated with a lower risk of lung cancer. β-Carotene was hypothesized to be largely responsible for the apparent protective effect, but this hypothesis was not supported by clinical trials.** ***Methods:*** **We examined the association between lung cancer risk and fruit and vegetable consumption in 77 283 women in the Nurses' Health Study and 47 778 men in the Health Professionals' Follow-up Study. Diet was assessed with the use of a food-frequency questionnaire that included 15 fruits and 23 vegetables. We used logistic regression models to estimate relative risks (RRs) of lung cancer within each cohort. All statistical tests were two-sided.** ***Results:*** **We documented 519 lung cancer cases among the women and 274 among the men. Total fruit and vegetable consumption was associated with a modestly lower risk of lung cancer among the women but not among the men. The RR for the highest versus lowest quintile of intake was 0.79 (95% confidence interval [CI] = 0.59–1.06) among the women and 1.12 (95% CI = 0.74–1.69) among the men after adjustment for smoking status, quantity of cigarettes smoked per day, time since quitting smoking, and age at initiation of smoking. However, total fruit and vegetable consumption was associated with a lower risk of lung cancer among never smokers in the combined cohorts, although the reduction was not statistically significant (RR = 0.63; 95% CI = 0.35–1.12 in the highest tertile).** ***Conclusion:*** **Higher fruit and vegetable intakes were associated with lower risks of lung cancer in women but not in men. It is possible that the inverse association among the women remained confounded by unmeasured smoking characteristics, although fruits and vegetables were protective in both men and women who never smoked. [J Natl Cancer Inst 2000;92: 1812–23]**

Worldwide, lung cancer has the highest incidence and mortality rates among all malignancies *(1)*, and smoking is known to be the primary cause *(2)*. Although of much less influence than tobacco use, consumption of diets high in fruits and vegetables have been associated with a lower risk of lung cancer in many studies *(1,3,4)*, in nonsmokers *(4,5)* as well as in smokers *(4)*. Much effort has been expended to identify the specific components of these foods that are responsible for the lower lung cancer risk. In the majority of studies, attention focused on the provitamin A carotenoids, particularly β-carotene *(6–9)*, because of their antioxidant properties and the historic importance of vitamin A in cell differentiation. The observed inverse association with dietary carotenoids is consistent with biochemical data showing lower serum levels of β-carotene in subjects who subsequently develop lung cancer *(10,11)*.

More recently, clinical trials of high doses of supplemental β-carotene did not produce the expected reductions in lung cancer risk *(12–14)*. Possible reasons for this lack of benefit include the following: 1) β-Carotene is the wrong protective constituent, 2) the high doses of β-carotene did not replicate the range of intake in epidemiologic studies, 3) the trials did not provide an early enough or sufficiently long period of exposure, 4) protection from fruits and vegetables in previous research has been overestimated because of inadequate control for smoking and its behavioral correlates, or 5) the case–control studies that constitute most of the literature were biased.

In 1991, the National Cancer Institute (Bethesda, MD) initiated the "5 A Day for Better Health" Program to promote increased consumption of fruits and vegetables *(15)* in response to the mounting evidence that these foods might reduce cancer risk at many sites and the public demand for timely guidance on cancer prevention. Since a number of micronutrients and phytochemicals in fruits and vegetables were potentially protective and the supplemental β-carotene trials were not yet completed, "5 A Day" focused on fruits and vegetables without specifying the critical protective factors. Thus, we examined whether adherence to this public health message was associated with a reduced risk of lung cancer in two prospective cohorts: the Nurses' Health Study (NHS) of women and the Health Professionals' Follow-up Study (HPFS) of men. We evaluated the importance of fruit and vegetable subgroups, numbers of servings per day, and variety in intake. We also evaluated the impact on risk estimates of repeat dietary assessments, the time elapsed between diet assessment and disease diagnosis, and the degree of control for various smoking characteristics.

Affiliations of authors: D. Feskanich, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; R. G. Ziegler, Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; D. S. Michaud, Department of Nutrition, Harvard School of Public Health, Boston; E. L. Giovannucci, W. C. Willett, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Departments of Nutrition and Epidemiology, Harvard School of Public Health; F. E. Speizer, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and Department of Environmental Health, Harvard School of Public Health; G. A. Colditz, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and Department of Nutrition and Harvard Center for Cancer Prevention, Harvard School of Public Health.

Correspondence to: Diane Feskanich, Sc.D., Channing Laboratory, 181 Longwood Ave., Boston, MA 02115 (e-mail: diane.feskanich@channing.harvard.edu).

See "Notes" following "References."

Subjects and Methods

Study Population

The NHS cohort was begun in 1976 with 121 700 female registered nurses, 30–55 years of age. Ten years later, the HPFS cohort was created with 51 529 male health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians), 40–75 years of age. The NHS was approved by the Institutional Review Board (IRB) of the Brigham and Women's Hospital, Boston, MA, and the HPFS received IRB approval from the Harvard School of Public Health, Boston. Both studies were designed to examine prospectively the effects of lifestyle on risk of chronic disease, particularly cancers and cardiovascular diseases. Information on individual characteristics and behaviors and newly diagnosed diseases is collected biennially on mailed questionnaires. A response rate of at least 90% was achieved for each biennial questionnaire. A food-frequency questionnaire (FFQ) was included in the NHS mailings in 1980, 1984, 1986, and 1990 and in the HPFS mailings in 1986 and 1990. Deaths are ascertained primarily through the National Death Index *(16)*.

The NHS and HPFS populations consisted of those participants who completed an acceptable FFQ at baseline (total energy intake of 600–3500 kcal/day for women and of 800–4200 kcal/day for men) and who had no previous report of cancer (except nonmelanoma skin cancer). After exclusions, 77 283 women remained in the NHS population and 47 778 men in the HPFS population.

Lung Cancer Cases

When a participant reported lung cancer on a biennial questionnaire, we attempted to obtain a medical record for confirmation and to establish a precise date of diagnosis. If the participant did not give permission or if we were otherwise unable to obtain the medical record, we relied on the verbal or written confirmation and the reported date of diagnosis from the participant. Lung cancers were also identified from death certificates; if possible, medical records were obtained for these reports.

From 1984 to 1996, 519 lung cancer cases were identified among the women in the NHS; 274 cases were identified among the men in the HPFS from 1986 to 1996. Four hundred fifty-eight (88%) of the cases in the NHS women and 255 (93%) of the cases in the HPFS men were confirmed by medical records; others were confirmed by the participant. Only six reported cases in the NHS were not confirmed to be lung cancer after review of the medical record; none of the HPFS lung cancer reports were disconfirmed. Cases with medical records were classified by cell type (adenocarcinoma, epidermoid/squamous carcinoma, small-cell carcinoma, large-cell carcinoma, combined epidermoid carcinoma and adenocarcinoma, carcinoid, or other).

Because of differences in cohort characteristics, there was a difference in the median age at diagnosis between the women (63 years) and the men (67 years).

Fruit and Vegetable Consumption

The initial 1980 FFQ for the NHS cohort contained only 61 foods, with 19 fruit and vegetable items. Subsequent FFQs in 1984, 1986, and 1990 were expanded to include 116 or more foods with 15 fruits and 30 vegetables (*see* Appendix Table 1). Therefore, we used the expanded 1984 FFQ as the baseline measure for the primary analyses in the NHS cohort. The HPFS participants received the expanded FFQ at study initiation in 1986 and again in 1990.

For each food, participants were asked to report their usual intake during the past year in terms of a standard serving size. Nine categories for frequency of consumption were provided, ranging from "never" to "6 or more per day." Nonresponse to an individual food item was considered to be a "never" response (<1% of the data for most foods).

The validity of the FFQ food consumption data was assessed previously by comparing the FFQ intakes for 127 men from the HPFS cohort with those reported for the same men on two 1-week diet records during the previous year *(17)*. The FFQ performed reasonably well in ranking individual fruit and vegetable intakes, with correlations between the two diet measures ranging from .95 for bananas to .25 for kale, mustard, or chard greens (mean $r = .57$). However, as is generally observed for foods perceived as healthy, the FFQ overestimated total fruit consumption by 85% and total vegetable consumption by 102% in comparison with the diet records. Also, the higher the number of fruits and vegetables on an FFQ, the greater the probability of overreporting their total intake *(18)*.

In this study, beans and lentils, tofu and soybeans, French fried potatoes, whole or mashed potatoes, and foods with small serving sizes (red chili sauce, garlic, and mushrooms) were not included in the measure of total vegetables. Total fruit included juices, since results were similar when juices were excluded. For the main analyses, we used a cumulative average measure of fruit and vegetable intake; i.e., in the NHS, the 1984 baseline measure was used to characterize follow-up from 1984 to 1986; an average of the 1984 and 1986 measures was used for follow-up from 1986 to 1990; and an average of the 1984, 1986, and 1990 measures was used for follow-up from 1990 to 1996. Cumulative averages were calculated similarly for the HPFS beginning with the 1986 baseline assessment. In secondary analyses, we applied various lag times between diet assessment and diagnosis of lung cancer. For example, for a lag of 4–8 years in the NHS, the 1984 diet was applied to follow-up from 1988 to 1990, the 1986 diet was applied to follow-up from 1990 to 1994, and the 1990 diet was applied to follow-up from 1994 to 1996.

In addition to frequency of consumption, we examined variety in fruit and vegetable intake. Any fruit or vegetable that was consumed at least once per week contributed 1 point toward a variety score. Items on the FFQ that were essentially the same food but in different forms (e.g., apples and apple juice or cooked spinach and raw spinach) contributed only 1 point if their combined intake was at least one per week. Variety scores ranged from 0 to 12 for fruits and from 0 to 19 for vegetables.

Smoking and Other Covariates

Current smoking status and quantity were reported on each biennial questionnaire. At baseline, participants were also asked about their smoking history. In analyses, we classified participants at the start of each 2-year follow-up cycle by smoking status (never, past, or current), quantity among current smokers (1–4, 5–14, 15–24, 25–34, 35–44, or ≥45 cigarettes smoked per day), time since quitting among past smokers (<5, 5–14, or ≥15 years in the NHS; <5, 5–9, or ≥10 years in the HPFS), and age at start of smoking (continuous variable in the NHS; <15, 15–19, 20–29, or ≥30 years in the HPFS). Age at start of smoking was not asked directly on any HPFS questionnaire but was inferred from the smoking history as the age category in which a participant first reported a number for cigarettes smoked per day.

Current weight was requested on all biennial questionnaires, and body mass index (BMI, kg/m^2) was calculated at each 2-year follow-up cycle with the use of the height reported at baseline. Physical activity was calculated as METs-hours per week (1 MET-hour is equivalent to 1 hour of sitting) from time spent in various leisure-time activities (e.g., walking, running, biking, or playing tennis) as reported on the 1986 questionnaire. Use of multivitamin supplements (yes or no) was ascertained in every 2-year follow-up cycle. Alcohol consumption (g/day) and total energy intake (kcal/day) were calculated from the baseline and follow-up FFQs.

Statistical Analysis

Study participants were followed from the return date of their baseline questionnaire (mailed June 1984 for the NHS and January 1986 for the HPFS) until a report of lung cancer, other cancer, or death or until the end of follow-up (June 30, 1996, for the NHS and January 31, 1996, for the HPFS).

The NHS and HPFS cohorts were analyzed separately. We used pooled logistic regression models *(19)* with 2-year follow-up cycles to estimate age-adjusted and multivariate-adjusted relative risks (RRs) of lung cancer. Indicator variables for nonresponse to a follow-up FFQ (1986 and 1990 FFQs in the NHS; 1990 FFQ in the HPFS) were included in the multivariate models. RRs were calculated for quintiles of dietary exposure (with the lowest quintile as the reference category) and for a linear increase of 1 serving/day. Risk estimates were also calculated by cell type and were stratified by age, smoking status, alcohol consumption, and multivitamin use. All statistical tests were two-sided.

To obtain a summary measure of results from the NHS and HPFS cohorts, a random effects model developed by DerSimonian and Laird *(20)* was used to combine the $\log_e$ risk estimates. This method was superior to an analysis of the combined raw data from the two cohorts because it accommodated differences in covariate data and follow-up periods.

RESULTS

Fruit and vegetable consumption was similar in the two cohorts. Based on the cumulative average consumption over follow-up, median fruit intakes were 2.0 and 2.1 servings/day and median vegetable intakes were 2.9 and 2.7 servings/day for the NHS and the HPFS, respectively. The six most frequently consumed fruits and vegetables were the same in both cohorts: iceberg lettuce, orange juice, tomatoes, apples or pears, carrots, and bananas. Participants reported moderate changes in fruit and vegetable intakes during the follow-up period. In a comparison of the total fruit and vegetable intake at baseline and in 1990, correlations were .61 in the NHS and .64 in the HPFS. Also, 52% of the women and 55% of the men who were in the top or bottom quintile at baseline remained in the same quintile in 1990.

Compared with the men in the HPFS cohort, the women in the NHS cohort were somewhat younger and a greater percentage of the women were current smokers, although they smoked fewer cigarettes per day and began smoking at a later age than the men (Table 1). In both cohorts, participants with higher fruit and vegetable intakes were older, were more physically active, consumed more calories, were more likely to take a multivitamin supplement, and were less likely to smoke. Among those who did smoke, a higher fruit and vegetable intake was associated with a lower quantity of cigarettes smoked; among past smokers, higher intake was positively associated with years since quitting. The median number of servings per day of fruits plus vegetables among never and current smokers was 5.2 and 4.3, respectively, in the NHS and 5.0 and 4.0, respectively, in the HPFS. Smoking rates in the NHS cohort were comparable to ones reported among U.S. women, but rates in the HPFS cohort were low compared with U.S. men. In the 1987 National Health Interview Survey *(21)*, 29% of adult women and 40% of adult men were current smokers; baseline rates in the NHS and HPFS cohorts were 24% and 10%, respectively.

Total Fruits and Vegetables

RRs of lung cancer for quintiles and continuous measures of fruit and vegetable consumption are listed in Table 2. All RRs were adjusted for age, follow-up cycle, availability of diet data from FFQs administered after baseline, total energy intake, and smoking characteristics (never, past, or current smoking status; years since quitting among past smokers; cigarettes smoked per day among current smokers; and age at start of smoking). Other measured covariates (i.e., BMI, physical activity, alcohol consumption, and use of multivitamin supple-

Table 1. Number of lung cancer cases during follow-up* and age-standardized characteristics at baseline by quintiles of total fruit and vegetable consumption among 77 283 women in the Nurses' Health Study (NHS) and 47 778 men in the Health Professionals' Follow-up Study

	Quintiles of total fruit and vegetable consumption				
	1	2	3	4	5
NHS women					
Lung cancer cases, No.	139	100	99	90	91
Age, mean y	49.3	50.4	51.0	51.7	52.3
Body mass index, mean kg/m^2	25.1	25.1	25.1	25.2	25.2
Physical activity, mean MET-hours†/wk	10.1	12.2	13.8	15.1	18.7
Energy intake, mean kcal/day	1446	1622	1753	1875	2013
Multivitamin user, %	32	35	37	40	43
Alcohol consumption, mean g/day	7.2	7.1	6.9	6.7	6.5
Smoking status and quantity‡					
Never, %	39	43	45	46	47
Past, %	27	31	33	34	35
Current, %	34	26	22	19	18
≥35 cigarettes/day,§ %	12	10	10	9	7
<5 y since quit smoking,‖ %	24	21	20	20	18
<15 y of age at start of smoking,¶ %	3	2	2	2	2
HPFS men					
Lung cancer cases, No.	62	47	56	55	54
Age, mean y	52.4	54.0	54.7	55.1	56.0
Body mass index, mean kg/m^2	25.7	25.6	25.5	25.4	25.4
Physical activity, mean MET-hours†/wk	14.2	16.6	18.8	20.9	25.6
Energy intake, mean kcal/day	1664	1838	1966	2105	2377
Multivitamin user, %	37	41	41	44	46
Alcohol consumption, mean g/day	12.7	12.1	11.6	10.5	9.8
Smoking status and quantity‡					
Never, %	39	43	46	47	49
Past, %	42	43	42	42	42
Current, %	16	11	8	7	6
≥35 cigarettes/day,§ %	20	16	12	12	10
<5 y since quit smoking,‖ %	24	21	20	18	17
<15 y of age at start of smoking,¶ %	13	12	11	10	12

*Follow-up was 1984 to 1996 for NHS and 1986 to 1996 for HPFS.

†MET values are for leisure-time activities and are scored in relation to a value of 1 MET-hour for 1 hour of sitting.

‡Categories of smoking status may not add up to 100% because of rounding and missing data.

§Quantity smoked was calculated among current smokers only.

‖Years since quit smoking was calculated among past smokers only.

¶Age at start of smoking was calculated among past and current smokers.

Table 2. Relative risks (RRs) of lung cancer by frequency of fruit and vegetable consumption in the Nurses' Health Study (NHS) and Health Professionals' Follow-up Study (HPFS) cohorts*

	Quintiles of consumption				1 additional serving/day, RR (95% CI‡)
	2	3	4	5	
Total fruits + vegetables†	Servings/day				
NHS women	3.4–4.5	4.6–5.6	5.7–7.2	>7.2	
HPFS men	3.2–4.3	4.4–5.4	5.5–7.2	>7.2	
	RR (95% CI‡)				
NHS women	0.79 (0.61–1.03)	0.77 (0.58–1.00)	0.76 (0.57–1.00)	0.79 (0.59–1.06)	0.95 (0.91–1.00)
HPFS men	0.83 (0.56–1.22)	0.99 (0.68–1.46)	1.08 (0.73–1.60)	1.12 (0.74–1.69)	1.04 (0.98–1.10)
Combined cohorts	0.80 (0.64–1.00)	0.84 (0.66–1.07)	0.88 (0.62–1.24)	0.91 (0.65–1.28)	0.99 (0.91–1.08)§
Total fruits	Servings/day				
NHS women	1.1–1.7	1.8–2.3	2.4–3.1	>3.1	
HPFS men	1.1–1.7	1.8–2.3	2.4–3.3	>3.3	
	RR (95% CI‡)				
NHS women	1.03 (0.80–1.32)	0.84 (0.64–1.12)	0.98 (0.74–1.29)	0.76 (0.56–1.02)	0.94 (0.87–1.02)
HPFS men	1.18 (0.80–1.73)	1.30 (0.88–1.92)	1.23 (0.82–1.84)	1.22 (0.80–1.87)	1.05 (0.95–1.16)
Combined cohorts	1.07 (0.87–1.32)	1.02 (0.67–1.57)	1.05 (0.84–1.32)	0.94 (0.59–1.49)	0.99 (0.89–1.10)
Total vegetables	Servings/day				
NHS women	1.9–2.5	2.6–3.2	3.3–4.3	>4.3	
HPFS men	1.7–2.3	2.4–3.0	3.1–4.1	>4.1	
	RR (95% CI‡)				
NHS women	0.73 (0.56–0.95)	0.73 (0.55–0.95)	0.86 (0.66–1.12)	0.68 (0.51–0.90)	0.94 (0.88–1.00)
HPFS men	1.18 (0.82–1.72)	0.97 (0.65–1.44)	1.10 (0.75–1.63)	1.04 (0.69–1.57)	1.03 (0.94–1.12)
Combinded cohorts	0.91 (0.57–1.47)‖	0.81 (0.62–1.06)	0.93 (0.74–1.17)	0.82 (0.54–1.25)	0.98 (0.90–1.07)
15 vegetables¶	Servings/day				
NHS women	0.9–1.2	1.3–1.6	1.7–2.1	>2.1	
HPFS men	0.8–1.1	1.2–1.5	1.6–2.1	>2.1	
	RR (95% CI‡)				
NHS women	0.97 (0.75–1.27)	0.98 (0.75–1.28)	0.91 (0.68–1.21)	0.86 (0.64–1.15)	0.92 (0.82–1.04)
HPFS men	0.98 (0.67–1.44)	1.11 (0.76–1.63)	0.87 (0.58–1.31)	1.20 (0.82–1.77)	1.11 (0.97–1.27)
Combined cohorts	0.98 (0.79–1.21)	1.02 (0.82–1.27)	0.90 (0.71–1.13)	0.99 (0.71–1.37)	1.01 (0.85–1.20)#

*Risks are calculated for quintile categories (quintile 1 is the referent) and for a linear increase in consumption of 1 serving/day. Results from the NHS and HPFS were pooled to obtain risk estimates for the combined cohorts. Risk estimates are adjusted for age, follow-up cycle, smoking status, years since quitting among past smokers, cigarettes smoked/day among current smokers, age at start of smoking, total energy intake, and availability of diet data after baseline measure.

†Total fruits and vegetables include all items on the food-frequency questionnaire (*see* Appendix Table 1) except tofu/soybeans, beans/lentils, red chili sauce, garlic, mushrooms, French fried potatoes, and potatoes (whole or mashed).

‡95% confidence interval.

§$P = .02$ in test for heterogeneity.

‖$P = .04$ in test for heterogeneity.

¶15 vegetables include string beans, broccoli, cabbage/cole slaw/sauerkraut, cauliflower, Brussels sprouts, corn, carrots, peas/lima beans, mixed vegetables, winter squash, eggplant/summer squash, yams/sweet potatoes, cooked spinach, kale/mustard or chard greens, and beets.

#$P = .05$ in test for heterogeneity.

ments) did not remain in the final models because they did not affect the RRs.

Among the women, the highest quintiles of intake for total fruits, total vegetables, and fruits and vegetables combined were associated with a 21%–32% lower risk of lung cancer, although only the vegetable results were statistically significant. In continuous models, an increase of 1 serving/day of fruits or vegetables was associated with a 6% lower risk. The inclusion of total energy intake in these models had minimal effect on the risk estimates (e.g., without controlling for total energy, RRs in highest quintiles were 0.77 for fruit and 0.69 for vegetables), but total energy intake was included to reduce error introduced by participants who consistently underreport or overreport foods on the FFQ. Correlations between fruits and vegetables and total energy intake were as follow: $r = .44$ for total fruits and vegetables, $r = .35$ for total fruits, and $r = .38$ for total vegetables.

In contrast to the findings in the women, we did not observe among the men a lower risk of lung cancer with higher fruit and/or vegetable intake. There was also no clear evidence of a decrease in risk when results from the two cohorts were combined. However, since the separate cohort results appear fairly heterogeneous, combining risk estimates may not be appropriate.

For vegetable consumption, we examined a limited group of 15 items that were likely to be the major vegetable component in a meal (thereby excluding tomatoes, tomato juice, tomato sauce, iceberg lettuce, romaine lettuce, raw spinach, alfalfa sprouts, and celery). We anticipated a stronger association with lung cancer for the remaining vegetables. Although the RR for an increase of 1 serving/day in the NHS cohort was marginally lower for the 15 vegetables than for all 23 vegetables, there was less evidence of an inverse association in quintile analyses. In the HPFS cohort, the association with lung cancer remained positive when the vegetable definition was limited to these 15 foods.

Although fruit and vegetable consumption was inversely associated with lung cancer among the women, the relationship did not appear linear in the quintile analyses. We examined fruit and vegetable intakes in both quadratic and cubic models, but neither provided a statistically significant improvement over the linear model. Fig. 1 illustrates the association in the NHS women when 5 servings/day of fruits plus vegetables is used as the reference group. Risk did not decrease with higher intakes and was significantly increased only among those consuming 2 or fewer servings/day (RR = 1.54; 95% confidence interval [CI] = 1.11–2.14).

Categories of Fruits and Vegetables

We examined various categories of fruits and vegetables (Table 3). Among the women, there were statistically significantly lower risks of lung cancer in the highest quintiles of intake for cruciferous vegetables, citrus fruits, and foods with a high total carotenoid content and nonsignificant, but noticeably lower, risks for foods high in vitamin C. Foods high in total carotenoids (≥2000 μg/serving) included ones high in lycopene (watermelon, grapefruit, tomatoes, tomato juice, and tomato sauce) or lutein (broccoli and romaine lettuce), as well as foods high in α- or β-carotene (cantaloupe, carrots, mixed vegetables, yams/sweet potatoes, raw or cooked spinach, and kale/mustard or chard greens). The RR in the highest quintile of intake for these foods was 0.73 (95% CI = 0.55–0.97), a lower point estimate of risk than that observed in the highest quintile of foods high in provitamin A carotenoids (≥2000 IU/serving) (RR = 0.82; 95% CI = 0.60–1.11). As seen for total fruits and vegetables, the results were different in the men. None of these fruit and vegetable categories was associated with a lower lung cancer risk in the HPFS cohort. In both men and women, no apparent benefit was evident from potatoes or legumes. A modest inverse association was observed for green leafy vegetables in the continuous analysis in both cohorts, but it was less evident in the quintile analyses.

Individual Fruits and Vegetables

Few specific fruits or vegetables demonstrated statistically significant protection against lung cancer, possibly because of the limited range of intakes for individual foods or the occurrence of protective factors in a variety of foods. Significantly lower risks were observed among the women for increases of 1 serving/day of apples and pears (RR = 0.63; 95% CI = 0.43–0.91), oranges (RR = 0.58; 95% CI = 0.37–0.91), and cauliflower (RR = 0.39; 95% CI = 0.16–0.92). Reductions were marginally significant for grapefruit (RR = 0.62; 95% CI = 0.37–1.04) and for grapefruit juice (RR = 0.31; 95% CI = 0.31–1.01). In the HPFS cohort, none of the individual fruits or vegetables were significantly associated with the risk of lung cancer. Tomato sauce (RR = 0.45; 95% CI = 0.23–0.91) and winter squash (RR = 0.36; 95% CI = 0.12–1.04) appeared protective when results from the two cohorts were combined, and an increase of one carrot per day conferred modest, but statistically not significant, protection (RR = 0.82; 95% CI = 0.59–1.16).

Population Subgroup Analyses

The differences in apparent effects of fruit and vegetable consumption on risk of lung cancer in the men's and women's cohorts were unexpected, and we attempted to explain the discrepancies by examining whether associations differed among various subgroups of the populations. Because smoking was strongly associated with lung cancer and was also more prevalent in the NHS cohort, we performed stratified analyses by smoking status. Among the NHS women, both fruits and vegetables appeared protective in each of the smoking subgroups, although fruits were most strongly associated with lower risk in the never smokers, whereas high vegetable intake conferred the lowest risk in current smokers (Table 4). In the HPFS, both fruits and vegetables appeared protective among the never smokers but not among the past or current smokers. When results among never smokers in the two cohorts were combined, the RR for

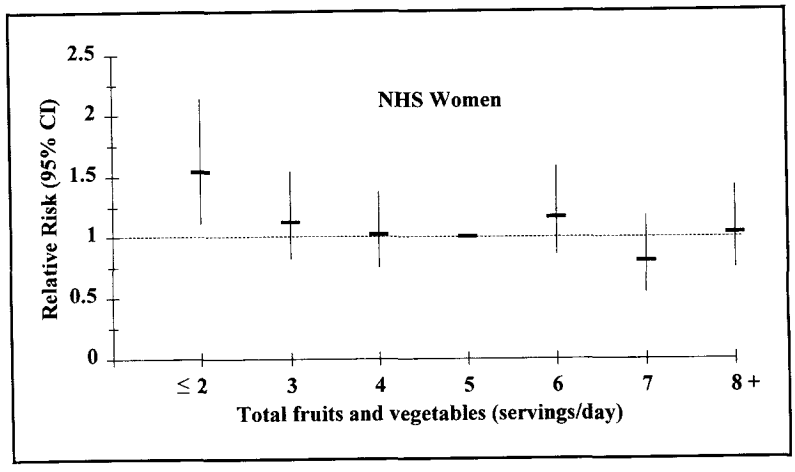

Fig. 1. Relative risk of lung cancer by number of servings of fruits and vegetables per day in the Nurses' Health Study (NHS) cohort of women. Five servings per day is the reference group. **Vertical bars** represent 95% confidence intervals (CIs). Risk estimates are adjusted for age, follow-up cycle, total energy intake, availability of diet data after baseline, smoking status, years since quitting among past smokers, cigarettes smoked per day among current smokers, and age at start of smoking.

Table 3. Relative risks (RRs) of lung cancer by frequency of consumption of various categories of fruits and vegetables in the Nurses' Health Study (NHS) and Health Professionals' Follow-up Study (HPFS) cohorts*

	Quintiles of consumption				1 additional serving/day, RR (95% CI‡)
	2	3	4	5	
Cruciferous vegetables†	Servings/wk				
NHS women	1.4–2.2	2.3–3.2	3.3–4.8	>4.8	
HPFS men	1.4–2.1	2.2–3.3	3.4–5.0	>5.0	
	RR (95% CI‡)				
NHS women	0.80 (0.62–1.05)	0.85 (0.65–1.12)	0.76 (0.57–1.01)	0.74 (0.55–0.99)	0.78 (0.59–1.04)
HPFS men	1.12 (0.76–1.64)	1.05 (0.72–1.53)	0.86 (0.57–1.30)	1.11 (0.76–1.64)	1.20 (0.88–1.63)
Green leafy vegetables§	Servings/wk				
NHS women	0.5–1.0	1.1–1.6	1.7–3.5	>3.5	
HPFS men	0.5–1.0	1.1–1.9	2.0–3.5	>3.5	
	RR (95% CI‡)				
NHS women	0.88 (0.66–1.18)	1.12 (0.86–1.46)	1.11 (0.85–1.47)	0.90 (0.68–1.20)	0.87 (0.66–1.15)
HPFS men	1.15 (0.77–1.72)	1.09 (0.74–1.59)	1.19 (0.80–1.79)	0.99 (0.65–1.49)	0.93 (0.63–1.38)
Potatoes‖	Servings/wk				
NHS women	1.0–1.9	2.0–2.9	3.0–3.9	>3.9	
HPFS men	1.0–1.9	2.0–2.9	3.0–4.0	>4.0	
	RR (95% CI‡)				
NHS women	0.98 (0.73–1.32)	1.11 (0.80–1.53)	1.02 (0.75–1.39)	1.09 (0.79–1.50)	1.20 (0.83–1.73)
HPFS men	0.83 (0.53–1.28)	1.04 (0.64–1.72)	1.13 (0.73–1.74)	1.05 (0.67–1.64)	1.16 (0.74–1.82)
Legumes¶	Servings/wk				
NHS women	0.5–1.0	1.1–1.4	1.5–2.0	>2.0	
HPFS men	0.7–1.3	1.4–1.8	1.9–3.1	>3.1	
	RR (95% CI‡)				
NHS women	0.81 (0.58–1.14)	0.93 (0.68–1.27)	1.09 (0.79–1.51)	1.07 (0.77–1.49)	1.20 (0.71–2.03)
HPFS men	1.05 (0.73–1.52)	1.47 (0.99–2.18)	0.84 (0.55–1.29)	1.21 (0.81–1.81)	1.10 (0.65–1.84)
Citrus fruits#	Servings/wk				
NHS women	2.0–3.9	4.0–6.8	6.9–9.0	>9.0	
HPFS men	2.0–4.4	4.5–7.0	7.1–9.8	>9.8	
	RR (95% CI‡)				
NHS women	1.03 (0.80–1.34)	0.85 (0.65–1.11)	0.98 (0.76–1.28)	0.72 (0.54–0.97)	0.84 (0.72–0.97)
HPFS men	0.97 (0.67–1.41)	0.87 (0.57–1.31)	0.79 (0.55–1.15)	1.12 (0.77–1.61)	1.03 (0.88–1.22)
Foods high in vitamin C**	Servings/wk				
NHS women	5.0–7.9	8.0–10.5	10.6–14.2	>14.2	
HPFS men	4.5–7.7	7.8–10.4	10.5–14.5	>14.5	
	RR (95% CI‡)				
NHS women	1.05 (0.81–1.35)	0.88 (0.67–1.15)	0.81 (0.61–1.08)	0.82 (0.62–1.10)	0.89 (0.80–1.00)
HPFS men	0.90 (0.61–1.32)	0.94 (0.64–1.37)	0.93 (0.63–1.38)	1.04 (0.71–1.53)	1.04 (0.91–1.19)
Foods high in total carotenoid††	Servings/day				
NHS women	6.8–9.4	9.5–12.4	12.5–16.9	>16.9	
HPFS men	6.4–9.4	9.5–12.6	12.7–17.4	>17.4	
	RR (95% CI‡)				
NHS women	0.69 (0.53–0.91)	0.76 (0.58–0.99)	0.77 (0.59–1.11)	0.73 (0.55–0.97)	0.95 (0.86–1.04)
HPFS men	1.15 (0.79–1.67)	1.09 (0.75–1.59)	0.80 (0.53–1.23)	1.18 (0.80–1.74)	0.99 (0.88–1.11)

*Risks are calculated for quintile categories (quintile 1 is the referent) and for a linear increase in consumption of 1 serving/day. Risk estimates are adjusted for age, follow-up cycle, smoking status, years since quitting among past smokers, cigarettes smoked/day among current smokers, age at start of smoking, total energy intake, and availability of diet data after baseline measure.

†Cruciferous vegetables include broccoli, cabbage/cole slaw/sauerkraut, cauliflower, Brussels sprouts, and kale/mustard or chard greens.

‡95% confidence interval.

§Green leafy vegetables include raw spinach, cooked spinach, kale/mustard or chard greens, and romaine lettuce.

‖Potatoes include French fried potatoes and potatoes (baked or mashed).

¶Legumes include peas/lima beans, tofu/soybeans, and beans/lentils.

#Citrus fruits include oranges, orange juice, grapefruit, and grapefruit juice.

**Foods high in vitamin C (≥30 mg/serving) include oranges, orange juice, grapefruit, grapefruit juice, other fruit juice, cantaloupe, strawberries, broccoli, and Brussels sprouts.

††Foods high in total carotenoid (≥2000 μg/serving) include cantaloupe, watermelon, grapefruit, carrots, broccoli, mixed vegetables, yams/sweet potatoes, raw spinach, cooked spinach, kale/mustard or chard greens, romaine lettuce, tomatoes, tomato juice, and tomato sauce.

lung cancer in the highest tertile of fruit plus vegetable intake was 0.63 (95% CI = 0.35–1.12).

We also examined lung cancers according to Kreyberg cell type *(22)* (Table 4). In the NHS cohort, total fruit and vegetable consumption appeared to be more protective for Kreyberg I tumors (squamous cell, small-cell, and large-cell carcinomas) than for Kreyberg II tumors (adenocarcinomas), the more common type among the women, although this distinction was less evident when fruits and vegetables were analyzed separately. Among the HPFS men, the risk estimates for high intakes of fruits, vegetables, and fruits and vegetables combined were all below 1 (although not statistically significant) for Kreyberg I and above 1 for Kreyberg II tumors.

Other analyses stratified by age, alcohol intake, and multivitamin use provided no evidence of a modification of effect. In both cohorts, associations between intake of fruits and vegetables and the risk of lung cancer were similar for participants over 65 years old and those 65 years old or younger, for abstainers and for drinkers of one or more drinks per day, and for current users and nonusers of multivitamins.

Variety in Fruit and Vegetable Consumption

In addition to frequency of consumption, we explored how variety in fruit and vegetable intake may contribute to the risk of lung cancer in the NHS women. Variety was calculated as the number of different fruits and vegetables that were consumed at least once per week. Risk of lung cancer was lower both for fruits (RR = 0.77; 95% CI = 0.55–1.20) and for vegetables (RR = 0.86; 95% CI = 0.66-.1.13) among women in the highest compared with the lowest quintile of the variety score (≥6 versus <2 for fruits; ≥10 versus <5 for vegetables). However, variety and frequency of consumption were highly correlated (r = .77 for fruits; r = .73 for vegetables). To assess the independent contribution of variety, we added frequency of consumption (in quintiles) to the models. For vegetables, the lower risk associated with variety was eliminated, whereas the RR for the highest quintile of frequency was similar to the estimate in the model without variety. For fruits, risk of lung cancer remained reduced for both variety (RR = 0.81; 95% CI = 0.55–1.20) and frequency (RR = 0.87; 95% CI = 0.60–1.28), suggesting that both factors contribute to a lower risk of cancer.

Timing and Number of Diet Measures

In our main analyses, fruit and vegetable intakes were calculated as cumulative averages of the diet data collected during follow-up. However, it is possible that earlier diet plays a more critical role in the etiology of lung cancer. To examine this possibility, we used various lag times between the diet measure and follow-up (Table 5). For both fruits and vegetables, a higher intake was not associated with a lower risk of lung cancer in men and was only weakly associated with a lower risk in women when diet was measured within 4 years of diagnosis. However, when a longer lag time was applied, inverse associations became apparent in both cohorts. With at least an 8-year lag between the diet measure and diagnosis, the RR in the highest quintile of total fruit and vegetable intake in the NHS was 0.72 (95% CI = 0.47–1.11), and the RR in the highest tertile of intake in the HPFS was 0.62 (95% CI = 0.29–1.35).

In the NHS, we also compared the use of single and multiple

Table 4. Relative risks (RRs)* (with 95% confidence intervals [CIs]) of lung cancer for high† fruit and vegetable consumption in the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS) cohorts by smoking status and cell type

	Never smokers	Past smokers	Current smokers
NHS women			
No. of cases	54	193	269
Total fruits + vegetables, RR (95% CI)	0.58 (0.28–1.18)	1.03 (0.63–1.71)	0.74 (0.49–1.12)
Total fruits, RR (95% CI)	0.34 (0.16–0.72)	0.78 (0.47–1.29)	0.89 (0.59–1.35)
Total vegetables, RR (95% CI)	0.94 (0.46–1.91)	0.85 (0.53–1.36)	0.59 (0.39–0.89)
HPFS men			
No. of cases	24	148	86
Total fruits + vegetables, RR (95% CI)	0.74 (0.27–2.04)	1.27 (0.72–2.22)	1.14 (0.54–2.41)
Total fruits, RR (95% CI)	0.59 (0.21–1.67)	1.34 (0.71–2.52)	1.54 (0.76–3.13)
Total vegetables, RR (95% CI)	0.57 (0.21–1.57)	1.12 (0.65–1.94)	0.95 (0.45–2.03)
	Kreyberg I‡	Kreyberg II‡	
NHS women			
No. of cases	179	232	
Total fruits + vegetables, RR (95% CI)	0.74 (0.46–1.21)	0.95 (0.62–1.48)	
Total fruits, RR (95% CI)	0.78 (0.48–1.26)	0.79 (0.49–1.25)	
Total vegetables, RR (95% CI)	0.63 (0.39–1.02)	0.76 (0.50–1.17)	
HPFS men			
No. of cases	120	93	
Total fruits + vegetables, RR (95% CI)	0.86 (0.48–1.64)	1.49 (0.75–2.98)	
Total fruits, RR (95% CI)	0.90 (0.47–1.73)	1.30 (0.65–2.58)	
Total vegetables, RR (95% CI)	0.86 (0.47–1.58)	2.08 (1.00–4.36)	

*Risks for never smokers are adjusted for age, follow-up cycle, total energy intake, and availability of diet data after baseline. In addition, risks for past smokers are adjusted for years since quitting, risks for current smokers are adjusted for cigaretts smoked/day, and risks for both past and current smokers are adjusted for age at start of smoking. Risks for Kreyberg cell type are adjusted for all of the above covariates.

†Quintile 5 is compared with quintile 1 in all analyses except those for never smokers, in which tertile 3 is compared with tertile 1 because of small numbers of cases.

‡Kreyberg I includes squamous cell, small-cell, and large-cell carcinomas; Kreyberg II includes adenocarcinomas.

Table 5. Relative risks (RRs)* (with 95% confidence intervals [CIs]) of lung cancer for high† fruit and vegetable consumption, with various lag times between diet assessment and follow-up in the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS) cohorts

Lag time	No. of cases	Follow-up	RR (95% CI)		
			Total fruits + vegetables	Total fruits	Total vegetables
			NHS women		
0–4 y	516	1984–1996	0.90 (0.66–1.21)	0.91 (0.67–1.24)	0.97 (0.73–1.29)
4–8 y	371	1988–1996	0.78 (0.56–1.10)	0.84 (0.59–1.20)	0.71 (0.52–0.99)
8–10 y	238	1992–1996	0.72 (0.47–1.11)	0.60 (0.38–0.95)	0.83 (0.55–1.25)
			HPFS men		
0–4 y	214	1986–1996	1.42 (0.92–2.21)	1.69 (1.07–2.67)	1.21 (0.80–1.82)
4–8 y	160	1990–1996	0.94 (0.54–1.63)	1.37 (0.79–2.36)	0.84 (0.49–1.45)
8–10 y	44	1994–1996	0.62 (0.29–1.35)	0.69 (0.31–1.54)	0.83 (0.34–2.05)

*Adjusted for age, follow-up cycle, total energy intake, smoking status, years since quitting among past smokers, cigarettes smoked/day among current smokers, and age at start of smoking.

†Quintile 5 is compared with quintile 1 in all analyses except those for HPFS men with 8–10 years' lag, in which tertile 3 is compared with tertile 1 because of small number of cases.

measures of diet assessed during follow-up from 1984 to 1996 prior to lung cancer diagnosis. We anticipated stronger associations with multiple measures, since they provide a better indication of long-term intake when diet is changing and can reduce measurement error in food intake when diet is stable. For vegetables, but not for fruits, the association was somewhat stronger with multiple measures. With the use of only the 1984 diet measure, the RR was 0.77 (95% CI = 0.59–1.02) in the highest quintile of vegetable intake, a weaker estimate than that obtained with the use of a cumulative average of the 1984, 1986, and 1990 diet measures (RR = 0.68; 95% CI = 0.51–0.90). A comparison of consistently high (quintile 5) to consistently low (quintile 1) vegetable intake in both 1980 and 1984 also showed a somewhat stronger association with lung cancer risk (RR = 0.71; 95% CI = 0.47–0.91) than that obtained with the use of the single 1984 diet measure.

Smoking as a Confounder

Because of the powerful influence of smoking on lung cancer incidence and the correlations between many smoking characteristics and diet, smoking is a strong confounder in associations between fruit and vegetable consumption and lung cancer risk and, therefore, must be assessed rigorously. Table 6 illustrates how the risk estimates for total fruit and vegetable consumption change with increasing control for smoking characteristics in the NHS and HPFS cohorts. With no control for smoking, the highest quintile of consumption was associated with a highly significant 57% lower risk of lung cancer in the women and a 44% lower risk in the men. These apparent benefits were greatly reduced (36% and 14% lower risks in women and men, respectively) when a simple measure of smoking status (never, past, or current) was added to the model. Risk estimates were further attenuated when past smokers were characterized by the time elapsed since quitting smoking and when current smokers were characterized by the number of cigarettes smoked per day. With both of these measures in the model, the lower risk of lung cancer in the highest quintile of total fruit and vegetable consumption in the women was further weakened to a nonsignificant 24%, and an inverse association was no longer evident in the men. The NHS risk estimate was further attenuated with the addition of age at which smoking was started, which provides a measure of smoking duration for both current and past smokers when current age and time elapsed since quitting are also in the model. From a public health perspective, any apparent beneficial effects of fruits and vegetables on lung cancer protection are small in comparison with

Table 6. Changes in relative risks (RRs)* of lung cancer by frequency of fruit and vegetable consumption with increasing detail in the smoking covariates in the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS) cohorts

Model	Smoking covariates	NHS women		HPFS men	
		Quintile 5,† RR (95% CI)	1 serving/day,‡ RR (95% CI)	Quintile 5,† RR (95% CI)	1 serving/day,‡ RR (95% CI)
1	None	0.43 (0.32–0.58)	0.87 (0.83–0.91)	0.56 (0.38–0.84)	0.94 (0.89–1.00)
2	Smoking status	0.64 (0.48–0.86)	0.92 (0.88–0.97)	0.86 (0.58–1.29)	1.00 (0.95–1.06)
3	Time since quitting	0.69 (0.51–0.92)	0.93 (0.89–0.98)	0.95 (0.63–1.42)	1.01 (0.96–1.07)
4	Current quantity	0.70 (0.52–0.95)	0.94 (0.90–0.98)	0.97 (0.65–1.47)	1.02 (0.96–1.08)
5	Time since quitting and current quantity	0.76 (0.57–1.02)	0.95 (0.91–0.99)	1.07 (0.71–1.61)	1.03 (0.98–1.09)
6	Age at start of smoking	0.79 (0.59–1.06)	0.95 (0.91–1.00)	1.12 (0.74–1.69)	1.04 (0.98–1.10)

*Model 1 is adjusted for age, follow-up cycle, total energy intake, and availability of diet data after baseline. Model 2 is adjusted for the covariates in model 1 plus smoking status (never, past, or current). Model 3 is adjusted for the covariates in model 2 plus time since quitting among past smokers. Model 4 is adjusted for the covariates in model 2 plus quantity among current smokers. Model 5 is adjusted for the covariates in models 3 and 4. Model 6 is adjusted for the covariates in model 5 plus age at start of smoking.

†Quintile 1 is the reference category.

‡Relative risk for a linear increase in consumption of 1 additional serving/day.

the harmful effects of smoking. This is illustrated in Fig. 2 with the NHS data.

Discussion

In this prospective study, both fruits and vegetables were associated with modestly lower risks of lung cancer among the women but not among the men. Risk was 21% lower in the highest compared with the lowest quintile of total fruit and vegetable consumption in the women but did not appear to decline in a dose-dependent manner. Lung cancer risk was fairly stable at intakes of 3 or more servings of fruits and vegetables per day but was significantly elevated among those consuming 2 or fewer servings per day. Limited numbers prevented us from examining lower intakes. Although the elevation in risk at low intake may be valid, the actual number of servings of fruits and vegetables may be inflated, as indicated by our validation study in which reported intakes for these food groups were higher from the FFQ than from the diet records. However, it is also possible that fruits and vegetables were underestimated by the two 1-week diet records if they did not capture full seasonal variation in consumption.

Although no individual food or food group was primarily responsible for the lower lung cancer risk in women, the most protection appeared to come from cruciferous vegetables, citrus fruits, and foods high in total carotenoids. This is consistent with the strong inverse associations for *Brassica* vegetables and citrus fruits that were reported recently from the Netherlands Cohort Study *(23)*. It is also consistent with our recent report *(24)* of a statistically significantly lower risk of lung cancer with high total carotenoid intake and a weaker inverse association with high intake of β-carotene. Inverse associations were also observed for green leafy vegetables and for foods high in vitamin C, but neither legumes nor potatoes were associated with a lower risk of lung cancer.

In contrast to the findings in women, there was little evidence of a lower risk of lung cancer with higher intakes of fruits and vegetables in men. Our results are similar to those from the Leisure World Study *(25)* in which an RR of 1.3 was reported for men in the highest tertile of fruit and vegetable intake, while these foods were protective in women. Although a few other studies have reported stronger results in women than in men *(26,27)*, research conducted among men has generally found clear inverse associations between fruit and vegetable intake and the risk of lung cancer *(4,28–31)*. We examined associations within each cohort by tumor cell type, since adenocarcinomas are more prevalent among women *(32)* and less influenced by smoking *(33)*, which might permit a clearer dietary effect. However, the inverse association between fruit and vegetable intake and lung cancer risk was stronger for the Kreyberg I tumors (squamous cell, small-cell, and large-cell carcinomas) in the women. Among the men, intake of fruits and vegetables exhibited inverse associations with the risk of Kreyberg I tumors and positive associations with the risk of Kreyberg II tumors (adenocarcinomas), which may explain the overall null association in the men, since 44% of the tumors were adenocarcinomas. Some previous studies *(23,34–36)* have noted stronger protective effects in Kreyberg I tumors; however, most studies *(4,26,27,37)* have found similar inverse associations with fruits and vegetables among cell types.

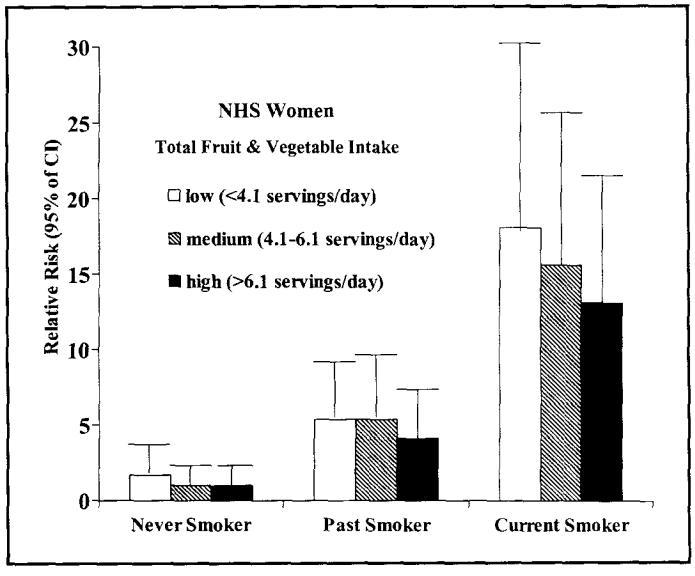

Fig. 2. Relative risk of lung cancer by smoking status and tertiles of total fruit and vegetable consumption in the Nurses' Health Study (NHS) cohort of women. Risk estimates are relative to never smokers in the highest fruit and vegetable tertile and are adjusted for age, follow-up cycle, availability of diet data after baseline, and total energy intake. CI = confidence interval.

Among the never smokers, fruits and vegetables were each associated with lower risks of lung cancer in both the men and the women, although statistical power in these analyses was low and results were nonsignificant. The apparent benefits among never smokers are most likely valid, since they are not attributable to uncontrolled confounding by smoking or negative behaviors associated with smoking. Among the men, the inverse associations for fruits and vegetables were limited to the never smokers; in contrast, among the women, the inverse associations were observed for past and current smokers as well. Thus, there is no persuasive evidence that effects are truly different among never and current smokers. Results of previous research *(4)* demonstrate clear effects in both subgroups, with some reports *(7,26,30,38)* suggesting stronger protective effects from fruits and vegetables among current smokers but others *(31,35,39)* suggesting stronger effects among never or past smokers.

Risk of lung cancer is very high among current smokers, and current smokers also tend to consume fewer fruits and vegetables *(21)*. In analyses with inadequate control for smoking characteristics, the observed benefits from intake of fruits and vegetables will be inflated. In our cohorts, the apparent risk reductions in the highest quintiles of fruit and vegetable consumption were severely attenuated among the women and were eliminated among the men when the number of cigarettes smoked per day among current smokers, time elapsed since quitting among past smokers, and age at start of smoking were added to a simple measure of smoking status in the multivariate models. It is also important to update smoking characteristics during follow-up in prospective studies because risk of lung cancer falls rapidly with smoking cessation and with decreases in smoking frequency *(40)*. Associations may still be confounded by the depth of inhalation, the choice of cigarette brand, and the exposure to passive smoking. It is possible that the remaining inverse association in our NHS cohort of women is largely due to confounding by unmeasured smoking characteristics.

Our study shows more modest benefits from intake of fruits and vegetables than many previous studies. Although risk estimates from case–control studies could be inflated by biased recall of diet among the case subjects and by selective participation of more health-conscious control subjects, results from retrospective and prospective studies have been quite similar. Discrepancies in study results are more likely explained by inadequate control for smoking. For example, in two prospective analyses that controlled only for smoking status (never, past, or current), the RR for lung cancer in the highest tertile of total fruit and vegetable intake was 0.60 for men in the Finnish Mobile Clinic Health Examination Survey *(31)* and 0.58 for women in the Leisure World Study *(25)*, similar to our risk estimates in the NHS cohort when only adjusted for smoking status. However, other prospective studies reported significantly lower risks of lung cancer with higher fruit and vegetable intakes even after controlling for pack-years of smoking: The RR in the highest quartile of intake was 0.49 among women in the Iowa Women's Health Study *(35)* and 0.52 among men and women in the First National Health and Nutrition Examination Survey (NHANES I) epidemiologic follow-up study *(38)*. Discrepancies in study results may also be explained by unmeasured characteristics of the study population (e.g., exposure to passive smoking), numbers of never versus current smokers in the study population, differences in dietary assessment methods, and varying composition of fruits and vegetables in measures of total intake.

Several cohort studies have noted an increased risk of lung cancer with higher alcohol intake *(41,42)*, particularly from beer and liquor *(42–44)*, after controlling for cigarette smoking, and in the Beta-Carotene and Retinol Efficacy Trial *(45)*, the increased risk of lung cancer in the intervention group was higher among those in the highest quartile of alcohol intake. However, our data did not support the hypothesis that alcohol or any individual alcoholic beverage is an independent risk factor for lung cancer, nor did alcohol confound or modify associations with fruits and vegetables. It is possible that we were unable to observe any associations because of the low alcohol consumption in the NHS and HPFS cohorts, where median intakes at baseline were 2.0 and 5.6 g/day, respectively.

A number of substances in fruits and vegetables may contribute to the lowering of lung cancer risk. Smoking causes oxidative damage in the lung *(46)*, and antioxidants such as carotenoids, vitamin C, and selenium may minimize this damage *(47,48)*. Higher intake of flavonoids has also been associated with reduced cancer risk *(49)*. However, the interactions among nutritional components are complex, and it is unclear when these dietary components are most effective in relation to the onset of disease. In both the NHS and HPFS cohorts, an inverse association between consumption of fruits and vegetables and risk of lung cancer became more apparent as the lag time between diet assessment and disease diagnosis increased. This observation raises the question about whether some of the β-carotene trials were of sufficient duration to see a beneficial effect. The appropriate timing between diet measurement and diagnosis is an unresolved issue, requiring further investigation with longer lag times.

Long-term consumption may also be an important factor in lung cancer etiology, as suggested by our stronger effect for consistently high vegetable intake with the use of two methods of integrating dietary information over time. The value of multiple measures was also demonstrated in the Zutphen Study *(50)*, in which consistently high intakes of fruits and vegetables on three assessments over a 10-year period before follow-up showed a much stronger association with risk of lung cancer than any one individual measure. In both cases, reduction in measurement error may also contribute to the stronger associations.

The prospective nature of the dietary data in this study makes it unlikely that fruit and vegetable intakes were biased by disease status. However, intake values were higher than reports from national surveys. For example, in the 1989–1991 Continuing Surveys of Food Intakes by Individuals *(51)*, the mean number of servings per day of fruits and vegetables (including potatoes and French fries) was 4.7 for men and 4.1 for women between 40 and 59 years of age. In our baseline cohorts, the mean number of servings per day (including potatoes and French fries) was 5.8 for the men and 5.7 for the women.

It is also unlikely that our results were attenuated by misclassification of cases. Most diagnoses of lung cancer were confirmed by medical records, and the high rate of confirmation (99%) lends support for the accuracy of the remaining cases that were based on self-report. A high response rate for each biennial questionnaire and the identification of lung cancer cases from death certificates among nonresponders minimize the likelihood that cases were missed.

In conclusion, risk of lung cancer was modestly lower with higher consumption of both fruits and vegetables in women but not in men. Control for detailed smoking characteristics substan-

Appendix Table 1. Fruits and vegetables and their standard serving sizes as listed on the Nurses' Health Study and the Health Professionals' Follow-up Study food-frequency questionnaire

Vegetable and serving size	Fruit and serving size
Tomatoes, 1 tomato	Raisins/grapes, 1 oz/bunch
Tomato juice, 4 fl oz	Prunes, ½ cup
Tomato sauce, ½ cup	Bananas, 1 banana
Red chili sauce,* 1 tbs	Cantaloupe, ¼ melon
String beans, ½ cup	Watermelon, 1 slice
Broccoli, ½ cup	Apples/pears, 1 item
Cabbage/cole slaw/sauerkraut, ½ cup	Apple juice, 6 fl oz
Cauliflower, ½ cup	Oranges, 1 orange
Brussels sprouts, ½ cup	Orange juice, 6 fl oz
Carrots, 1 carrot/½ cup	Grapefruit, ½ grapefruit
Mixed vegetables, ½ cup	Grapefruit juice, 6 fl oz
Corn, 1 ear/½ cup	Other fruit juices, 6 fl oz
Peas/lima beans, ½ cup	Strawberries, ½ cup
Winter squash, ½ cup	Blueberries, ½ cup
Eggplant/summer squash, ½ cup	Peaches/apricots/plums, 1 item
Yams/sweet potatoes, ½ cup	
Beets, ½ cup	
Spinach, cooked, ½ cup	
Spinach, raw, 1 cup	
Kale/mustard or chard greens, ½ cup	
Iceberg lettuce, 1 cup	
Romaine lettuce, 1 cup	
Celery, 4-inch stick	
Mushrooms,* 1 mushroom	
Garlic,* 1 clove	
Alfalfa sprouts, ½ cup	
Beans/lentils,* ½ cup	
Tofu/soybeans,* 3–4 oz	
French fried potatoes,* 4 oz	
Potatoes, whole/mashed,* 1 potato/1 cup	

*Foods not included in analysis of total vegetables.

tially attenuated the initially estimated protective effects, and it is possible that the inverse association among the women remains confounded by inadequately measured smoking patterns. However, total fruit and vegetable intake appeared protective against lung cancer among both men and women who never smoked. Further investigation is needed to characterize the strength of the association, its generalizability, the dose–response relationship, and the timing of diet in relation to diagnosis. Although the "5 A Day" Program promotes a reasonable and prudent diet that is beneficial for health, it is necessary to continue the evaluation of these recommendations in terms of specific health outcomes.

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NOTES

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